



PCT/CH 03 / 00750

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21 October 2003

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Patents Form 1/77

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THE PATENT OFFICE

14 NOV 2002

14NOV02 1763409-1 D1014
P01/7700 0.00-0226550.2

Request for grant of a patent
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The Patent Office

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Newport
South Wales
NP10 8QQ

Confirmation by Mail

1. Your reference

30076GB

14 NOV 2002

2. Patent application number

(The Patent Office will fill in this part)

0226550.2

3. Full name, address and postcode of the or of
each applicant (underline all surnames)Givaudan SA
Chemin de la Parfumerie 5
1214 Vernier
Switzerland

Patents ADP Number (if you know it)

8408031001

If the applicant is a corporate body, give the
country/state of its incorporation

Switzerland

4. Title of the Invention

Organic Compounds

5. Name of your agent (if you have one)

"Address for service" in the United Kingdom
to which all correspondence should be sent
(including the postcode)

Patents ADP number (if you know it)

6. If you are declaring priority from one or more
earlier patent applications, give the country
and the date of filing of the or of each of these
earlier applications and (if you know it) the or
each application number

Country

Priority application number
(if you know it)Date of filing
(day/month/year)7. If this application is divided or otherwise
derived from an earlier UK application,
give the number and the filing date of
the earlier application

Number of earlier application

Date of filing
(day/month/year)8. Is a statement of inventorship and of right
to grant of a patent required in support
of this request? (Answer 'Yes' if:)

yes

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an
applicant, or

c) any named applicant is a corporate body.

See note (d)

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9. Enter the number of sheets for any of the following items you are filing with this form.
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Description 29

Claim(s) 2

Abstract 1

Drawing(s)

10. If you are also filing any of the following, state how many against each item.

Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (Patents Form 7/77)

Request for preliminary examination and search (Patents Form 9/77) 1

Request for substantive examination (Patents Form 10/77)

Any other documents
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11. I/We request the grant of a patent on the basis of this application.

Signature

Date 14/11/02

12. Name and daytime telephone number of person to contact in the United Kingdom

Colin Brown (office time) Tel. No: 01/784417721

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Notes

- a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 08459 500505
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DUPLICATE

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Organic Compounds

This invention is concerned with compounds useful for the prevention or suppression of human malodour, in particular human axillary malodour.

It is known that fresh sweat is odourless and that odour is only formed upon contact of sweat with skin bacteria (for example bacteria of the genera of *Staphylococcus* and *Corynebacteria*) and it is believed that odourless molecules present in sweat are degraded by bacteria colonising the axilla. It is generally accepted (Labows *et. al.*, Cosmet. Sci Technol. Ser. (1999), 20:59-82) that highly unpleasant malodour is released from fresh sweat mainly by the *Corynebacteria* genus of bacteria. The principal constituents thought to be responsible for malodour include volatile steroids, volatile sulphur compounds and short-chain, branched fatty acids.

It has been suggested to treat malodour by eradicating the bacteria responsible for causing the odour. Indeed, commercially available cosmetic deodorants often contain antibacterial compounds that generally inhibit the growth of skin microflora. Antibacterial compounds currently used in deodorant products include, for example Triclosan (2,4,4'-trichloro-2'-hydroxy-diphenyl-ether). However, a draw-back to the use of antibacterials is the potential for disturbing the equilibrium of the skin's natural microflora.

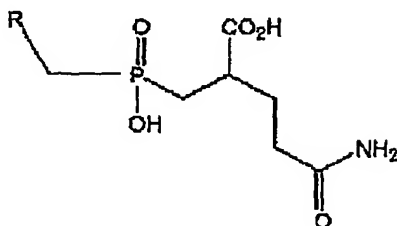
Fatty acids, in particular short chain, branched fatty acids are known to play a role in axillary malodour, and are particularly foul smelling components of stale sweat. In co-pending application PCT/CH0200262 the applicant has disclosed an enzyme that mediates in a process of transforming odourless compounds found in sweat into these malodorous fatty acids. In this co-pending application there is also disclosed a broad class of compounds having activity as inhibitors of the enzyme.

Nevertheless there remains the need to find further compounds displaying good inhibitory properties with respect to the above mentioned enzyme.

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Accordingly, the invention provided in a first aspect a compound of formula (I)



wherein R is a substituted alkyl, benzyl or allyl residue selected from the group consisting of

nonyl;

4,4,4-trifluoro-propyl;

2-methyl-4-phenyl-butyl;

4-trifluoromethyl-phenyl;

pentafluorophenyl;

4-fluoro-phenyl;

naphthalene-2-yl;

biphenyl-2-yl;

4-tert-butyl-phenyl;

5,5,7,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalene-2-yl;

5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl;

1,1,3,3-tetramethyl-indan-5-yl;

styryl;

2,6-dimethyl-hept-1,5-dienyl;

2-(4-tert-Butyl-phenyl)-1-methyl-vinyl;

2-(4-Isopropyl-phenyl)-1-methyl-vinyl;

1-Methyl-3-(2,2,3-trimethyl-cyclopent-3-enyl)-propenyl;

2-(4-Isobutyl-phenyl)-1-methyl-vinyl;

2-(2-isopropyl-phenyl)-1-methyl-ethenyl;

2-phenyl-ethyl;

cyclohexyl-methyl;

2,2-dimethyl-propyl;

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2-pentafluorophenyl-ethyl;
3-phenyl-propyl; heptyl; and
4-isopropyl-cyclohex-1-enyl.

Compounds of the formula (I) contain chiral atoms and as such they can exist as isomeric mixtures or they may exist as pure stereoisomers. Most preferred are compounds have an S-configuration on the carbon atom in the position alpha to the carboxyl group.

As stated herein above, compounds of the present invention may interact with an enzyme thereby to reduce the enzyme's ability to cleave compounds in sweat leading to release of malodorous acids from odourless fresh sweat. That enzyme, described in the afore-mentioned co-pending application, was isolated from the bacteria of the genus *Corynebacteria* that can be found colonising the axilla, in particular certain *Corynebacteria sp.*, more particularly *Corynebacteria striatum* Ax 20 which has been submitted on the 26, April 2001 to the International Depository Authority DSMZ-Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH, D-38124 Braunschweig. The Accession Number provided by the International Depository Authority is DSM 14267. The enzyme was found to occur intracellularly and can be released from the cells by mechanical disruption of the cell envelope. Thus, it may be isolated from cellular extracts obtained from wild-type bacterial strains, especially from strains of *Corynebacteria* isolated from the human axilla, in particular *Corynebacterium striatum* Ax 20. In the alternative, it may be produced by recombinant means which are well known to persons skilled in the art.

The amino acid sequence of this enzyme is set forth in SEQ ID No. 1 and a nucleic acid sequence encoding for this enzyme is set forth in SEQ ID No. 2, both of which sequences are shown below.

Compounds of the present invention display inhibition of the enzyme at concentrations of about 1 to 500, nanomolar more particularly from nanomolar to tens of nanomolar concentration in vitro, e.g. from 10 to 20 nanomolar. Furthermore, having regard to the

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lipophilicity of the residue R, the compounds are adapted to penetrate the cell walls of the enzyme-producing bacteria, as such, they are efficacious in vivo.

Indeed, the nature of the residue R appears to influence the ability of compounds to penetrate the cellular walls of different bacteria colonising the axilla and which are implicated in malodour production. For example, other strains of *Corynebacteria*, or bacteria of the genus *Staphylococci* found in the microflora of the axilla also produce related enzymes that themselves mediate in biochemical reactions wherein L-glutamine derivatives are cleaved at N α . The compounds of the present invention may interfere in cellular processes of a wide variety of bacterial strains thereby resulting in the suppression or prevention of malodour from these sources.

The in vitro activity of the compounds as inhibitors may be measured in terms of either their IC_{50} values or their K_i values, both of which measures are well known to the person skilled in the art. As is well known, the IC_{50} value provides the concentration of an inhibitor needed to reduce enzyme velocity by half at a given substrate concentration. This value is dependent on the affinity of the substrate for the enzyme which is reflected in the value K_m of the substrate. In this way, the K_i value may be determined for a given substrate and a given substrate concentration by measuring IC_{50} and then calculating according to the following formula

$$K_i = \frac{IC_{50}}{1 + \frac{[Substrate]}{K_m}}$$

The uptake of the compounds in bacterial cells and the inhibition of the enzyme contained therein may be measured using an assay based on stationary-phase living cells. Thus, cells may be incubated along with inhibitory compound or compounds, and the substrate (i.e. the material found in sweat, which when cleaved by the enzyme forms the malodorous acids), and the release of acids may be measured at various inhibitor concentrations. By comparing IC_{50} values obtained with the living cells with the IC_{50}

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values obtained with the isolated enzyme the ease of penetration of the compounds into the bacterial cells can be assessed.

Compounds of the present invention may be added to any cosmetic and personal care products such as sticks, roll-ons, pump-sprays, aerosols, deodorant soaps, powders, solutions, gels, creams, sticks, balms and lotions to enhance the deodorising effect of these products. Preferably, a compound of the present invention may be employed in said products in amounts of about 0.01 to 0.5% by weight.

The above-mentioned products, in addition to the inhibitors, may comprise anti-bacterial agents known in the art, e.g. Triclosan. The products may also comprise dermatologically acceptable ingredients such as are commonly used in these types of product. Examples of such additional ingredients include fragrances, colorants, opacifiers, buffers, antioxidants, vitamins, emulsifiers, UV absorbers, silicones and the like. As is also well known, all products can be buffered to the desired pH.

In addition to the inhibitor, a deodorant cologne may comprise ethanol and fragrance. Fragrance may be present from 1 to 10% and the ethanol can be present to make up the mass to 100%.

Additional ingredients in a typical ethanol-free deodorant stick may include polyols, such as propylene glycol; derivatives thereof, such as propylene-glycol-3-myristyl ether (Witconol APM); water; a surfactant such as sodium stearate; and a fragrance. The polyol may be present in an amount of 30 to 40%; the derivatives of the polyol likewise may be present at about 30 to 40%; water may be present to about 10 to 20%; the surfactant may be present to 5 to 10%; and the fragrance may be present in an amount mentioned above.

A typical antiperspirant stick might contain as additional ingredients such as Ethylene Glycol Monostearate (e.g. from 5 to 10%); Shea butter (e.g. from 3 to 5%); Neobee 1053 (PVO International) (e.g. from about 12 to 15%); Generol 122 (Henkel) (e.g. from

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about 3 to 7%); Dimethicone (DC 345)(e.g. from 30 to 40%); aluminium sesquichlorohydrate (e.g. from about 15 to 20%); and a fragrance, e.g. from 1 to 10%.

An antiperspirant aerosol may contain ethanol, e.g. from about 10 to 15%; zirconium aluminium tetrachlorohydrate, e.g. from about 3 to 5%; Bentone 38, e.g. from about 1 to 2%; fragrance in an amount aforementioned; and a hydrocarbon propellant, e.g. S-31 up to 100%.

An antiperspirant pump composition may contain aluminium sesquichlorohydrate, e.g. from 15 to 25%; water, e.g. from 50 to 60%; Triton X-102 (Union carbide), e.g. from 1 to 3%; dimethyl Isosorbide (ICI), e.g. from 15 to 25 %; and a fragrance in an amount as aforementioned.

All percentages mentioned above are in wt %.

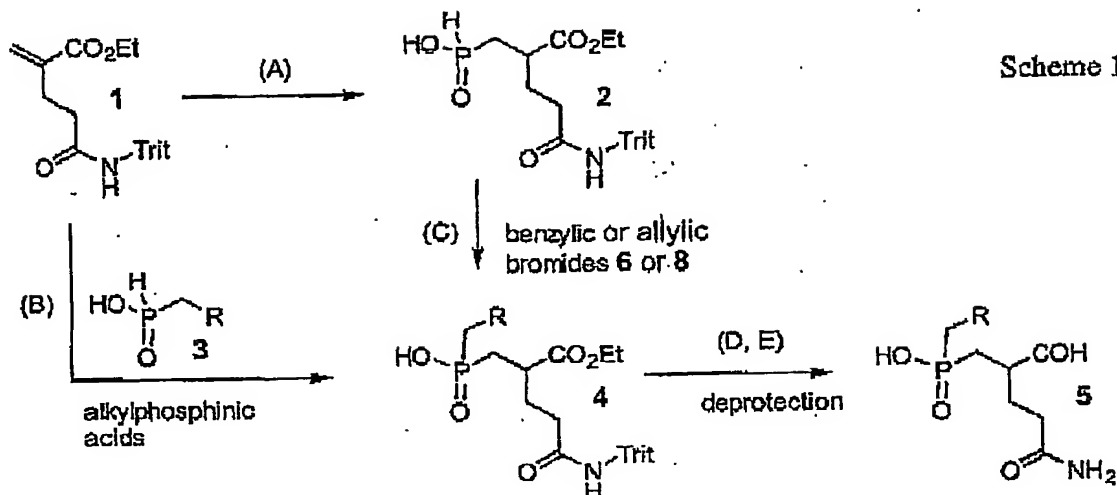
Accordingly, the present invention relates to the use of the compounds and/or compositions containing same for the elimination or suppression of malodour. The invention also relates to compositions comprising an odour suppressing quantity of an inhibitor of the enzyme and dermatologically acceptable vehicles which are generally well known in the art of cosmetic and personal care products.

The invention also provides in another of its aspects, a method of suppressing axillary malodour comprising the step of providing a composition for application to a person in need of treatment, said composition containing an inhibitor compound and dermatologically acceptable vehicle therefor, said compound being selected from one or more compounds described above.

A compound of formula (I) may be prepared according to synthetic protocols as set out in detail below with reference to Scheme 1, Scheme 2 and the Examples

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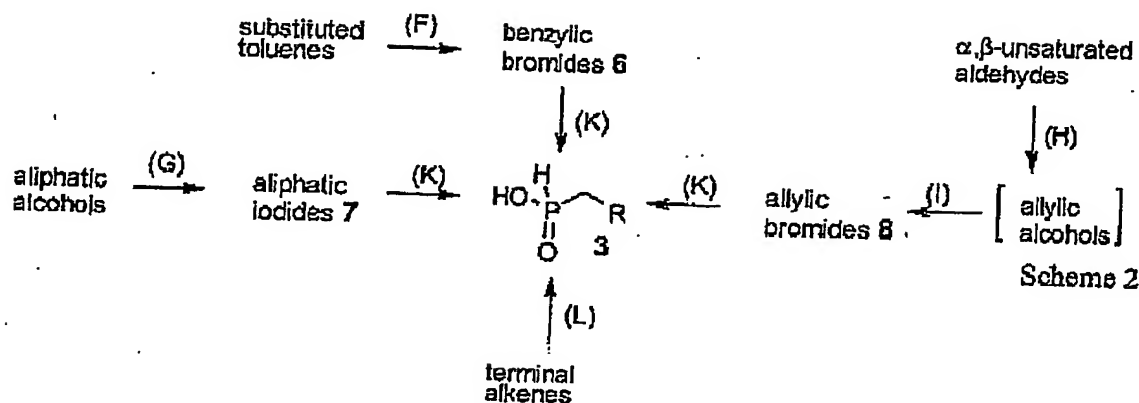
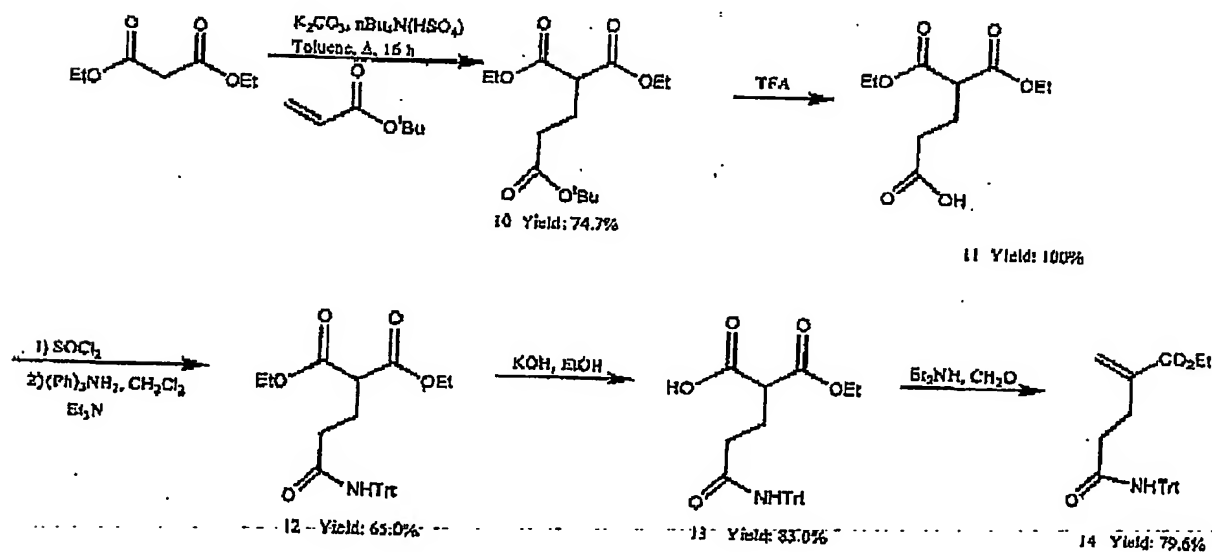
- A) 5 equivalents (eq.) $\text{HP}(\text{OTMS})_2$, for 2 h at 130°C ;
- B) 1 eq alkylphosphonic acid 3, 5 eq HMDS for 3 h at 130°C , then 1 eq acrylate 1 for 4 h at 130°C , then EtOH at 70°C . The product is obtained in quantitative yield.
- C) 1 eq benzylic or allylic bromide (6 or 8), 3 eq BSA, at 25°C . The product is obtained in quantitative yield.
- D) 1 N LiOH / EtOH 1:1 (weight-equivalents) for 1 day at 25°C to give the product in quantitative yield.
- E) 2.2 eq $(i\text{Pr})_3\text{SiH}$ in TFA at 25°C for 3 h to provide compounds of the present invention.

The acrylate starting material (1) may be formed according to a method described in co-pending application PCT/CH0200262 and is set forth in Scheme 3 below.

The alkyl, benzyl or allyl halides are either commercially available or may be formed from commonly available starting materials according to synthetic protocols known per se and set out in Scheme 2 below.

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F) 1 eq Br₂ at 170°C for 4 h.G) 2 eq Pyridine, 1.2 eq PPh₃, 1.2 eq Iodine at 0°C for 2 h.H) 0.35 eq NaBH₄, MeOH for 2 h at 0°C, to provide the allyl alcohols in quantitative yield.I) Et₂O, 0.4 eq PBr₃ for 5 h at 0°C to provide allyl bromides in quantitative yields.K) 3-5 eq HP(OTMS)₂ in CH₂Cl₂, for 16 h.L) 2 eq NaH₂PO₂(H₂O), 1 eq BEt₃, MeOH for 6 h at 25°C.

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There now follows a series of Examples that serve to illustrate the invention.

Synthesis Examples 1 to 9

The following compounds are formed according to the following syntheses:

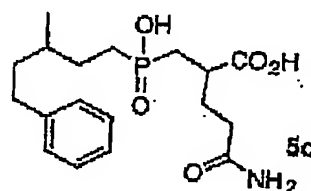
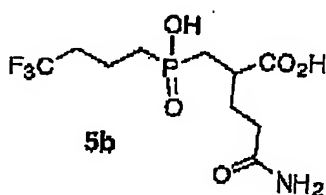
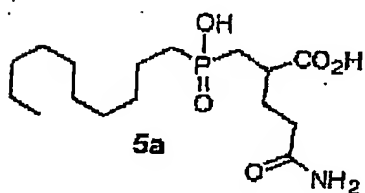
- 5a 4-Carbamoyl-2-(decyl-hydroxy-phosphinoylmethyl)-butyric acid
- 5b 4-Carbamoyl-2-[hydroxy-(4,4,4-trifluoro-butyl)-phosphinoylmethyl]-butyric acid
- 5c 4-Carbamoyl-2-[hydroxy-(3-methyl-5-phenyl-pentyl)-phosphinoylmethyl]-butyric acid
- 5d 4-Carbamoyl-2-[hydroxy-(4-trifluoromethyl-benzyl)-phosphinoylmethyl]-butyric acid
- 5e 4-Carbamoyl-2-(hydroxy-pentafluorophenylmethyl-phosphinoylmethyl)-butyric acid
- 5f 4-Carbamoyl-2-[(4-fluoro-benzyl)-hydroxy-phosphinoylmethyl]-butyric acid
- 5g 4-Carbamoyl-2-(hydroxy-naphthalen-2-ylmethyl-phosphinoylmethyl)-butyric acid
- 5h 2-(Biphenyl-2-ylmethyl-hydroxy-phosphinoylmethyl)-4-carbamoyl-butyric acid
- 5i 2-[(4-tert-Butyl-benzyl)-hydroxy-phosphinoylmethyl]-4-carbamoyl-butyric acid
- 5j 4-Carbamoyl-2-[hydroxy-(5,5,7,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-ylmethyl)-phosphinoylmethyl]-butyric acid
- 5k 4-Carbamoyl-2-[hydroxy-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-ylmethyl)-phosphinoylmethyl]-butyric acid
- 5l 4-Carbamoyl-2-[hydroxy-(1,1,3,3-tetramethyl-indan-5-ylmethyl)-phosphinoylmethyl]-butyric acid
- 5m *E*-4-Carbamoyl-2-[hydroxy-(3-phenyl-allyl)-phosphinoylmethyl]-butyric acid
- 5n *E*-4-Carbamoyl-2-[(3,7-dimethyl-octa-2,6-dienyl)-hydroxy-phosphinoylmethyl]-butyric acid

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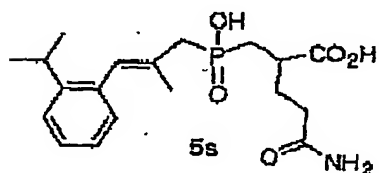
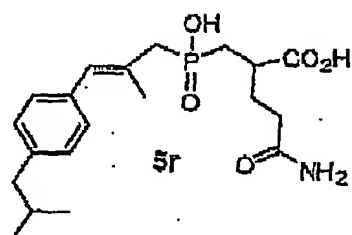
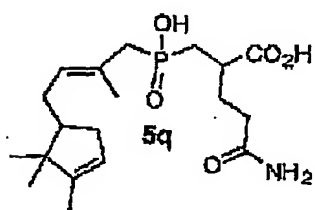
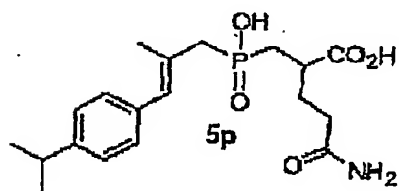
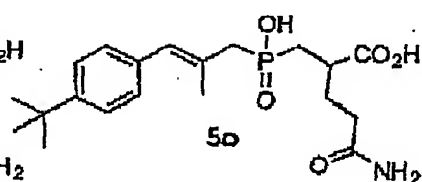
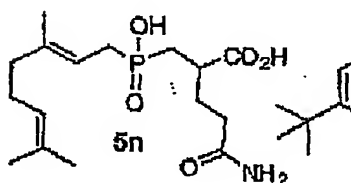
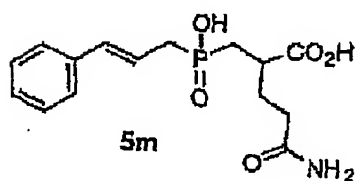
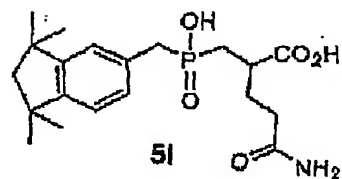
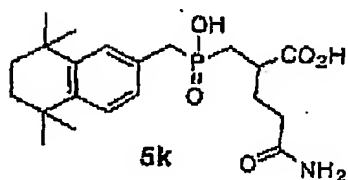
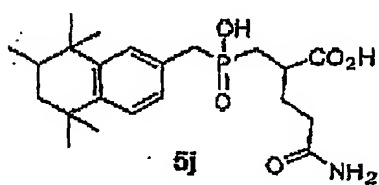
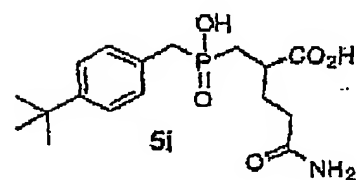
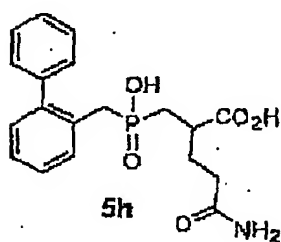
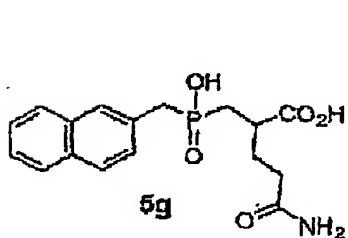
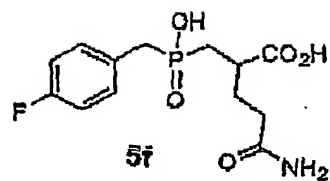
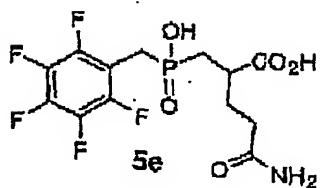
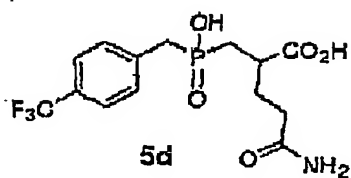
- 5o *E*-2-{{3-(4-tert-Butyl-phenyl)-2-methyl-allyl}-hydroxy-phosphinoylmethyl}-4-carbamoyl-butyric acid
- 5p *E*-4-Carbamoyl-2-{hydroxy-[3-(4-isopropyl-phenyl)-2-methyl-allyl]-phosphinoylmethyl}-butyric acid
- 5q *E*-4-Carbamoyl-2-{hydroxy-[2-methyl-4-(2,2,3-trimethyl-cyclopent-3-enyl)-but-2-enyl]-phosphinoylmethyl}-butyric acid
- 5r *E*-4-Carbamoyl-2-{hydroxy-[3-(4-isobutyl-phenyl)-2-methyl-allyl]-phosphinoylmethyl}-butyric acid
- 5s *E*-4-Carbamoyl-2-{hydroxy-[3-(2-isopropyl-phenyl)-2-methyl-allyl]-phosphinoylmethyl}-butyric acid
- 5t 4-Carbamoyl-2-[hydroxy-(3-phenyl-propyl)-phosphinoylmethyl]-butyric acid
- 5u 4-Carbamoyl-2-[(2-cyclohexyl-ethyl)-hydroxy-phosphinoylmethyl]-butyric acid
- 5v 4-Carbamoyl-2-[(3,3-dimethyl-butyl)-hydroxy-phosphinoylmethyl]-butyric acid
- 5w 4-Carbamoyl-2-[hydroxy-(3-pentafluorophenyl-propyl)-phosphinoylmethyl]-butyric acid
- 5x 4-Carbamoyl-2-[hydroxy-(4-phenyl-butyl)-phosphinoylmethyl]-butyric acid
- 5y 4-Carbamoyl-2-(hydroxy-octyl-phosphinoylmethyl)-butyric acid
- 5z 4-Carbamoyl-2-[hydroxy-(4-isopropyl-cyclohex-1-enylmethyl)-phosphinoylmethyl]-butyric acid

Structures of these compounds are set out below:



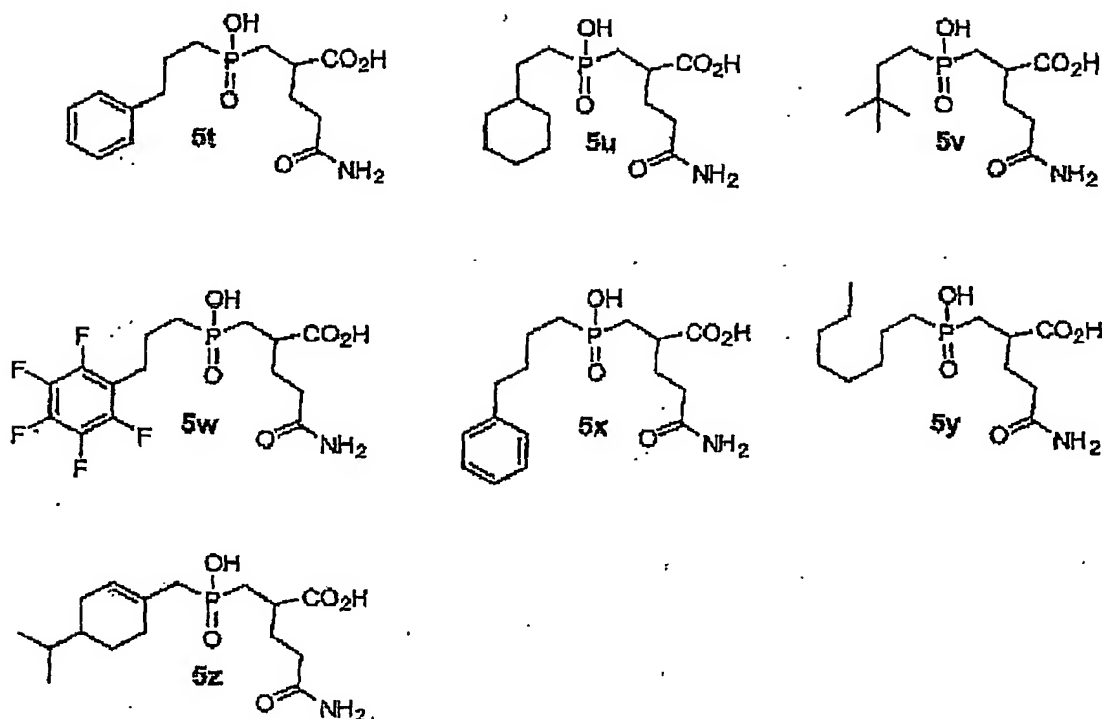
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The following Examples are described with reference to Scheme 1 and Scheme 2.

Example 1

Preparation of 2-Hydroxyphosphinoylmethyl-4-(trityl-carbamoyl)-butyric acid ethyl ester 2: (Step A of Scheme 1)

The synthesis is carried out analogously to L.A.Reiter, B.P.Jones, *J.Org.Chem.* 62, 2808 (1997) or W.P.Malachowski, J.K.Coward, *J.Org.Chem.* 59, 7625 (1994).

In a 500mL flask equipped with a septum and a condenser, 25 g (0.3 mol) ammonium phosphinate and 49 g (0.3 mol) HMDS are heated under N₂ at 110°C for 3.5 h. The reaction mixture is cooled to 5°C where 25 g acrylate 1 (the synthesis of which is set out

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in Scheme 3 above) in 150 ml dichloromethane are added. The mixture is stirred for 16 h at room temperature. Work-up: 1 N HCl and CH_2Cl_2 are added. The organic phase is washed with 1 N HCl, the combined acidic phases are re-extracted with CH_2Cl_2 . The combined organic phases are dried over MgSO_4 , evaporated under reduced pressure and dried at 50°C under high vacuum yielding 28.8 g (99.9%) of phosphinic acid 2.

Yield: 99.9%

M.p.: $152-154^\circ\text{C}$ (white solid).

Purity: 89 % (^{31}P -NMR)

^{31}P -NMR (CDCl_3 , 400MHz): 32.0 ppm (s).

MS (ESI neg.): 957 [2M - H], 478 [M - H].

^1H -NMR (CDCl_3 , 400MHz): 1.2 (t, 3H), 1.8 (m, 1H), 1.9 (2H), 2.05 (m, 1H), 2.25 (m, 1H), 2.7 (m, 1H), 4.1 (q, 2H), 6.3 - 7.7 (d, 1H, P-H, $J = 560$ Hz), 6.9 (s, 1H, NH), 7.2 (15H, trityl-H), 8.2 (1H, P-OH).

^{13}C -NMR (CDCl_3 , 400MHz): 14.2 (CH_3), 28.7 (d, CH_2), 30.8, 31.8 (d, P- CH_2), 34.3 (s, CH_2), 38.2 (CH), 61.2 (OCH_2), 70.5 (Ph_3C), 127.0 (3C, Trityl-CH), 127.9 (6C, Trityl-CH), 128.7 (6C, Trityl-CH), 144.6 (3C, Trityl-C), 171.0 (C=O), 174.0 (C=O).

Example 2

Preparation of 4-Carbamoyl-2-[hydroxy-(4,4,4-trifluoro-butyl)-phosphinoylmethyl]-butyric acid 4b: (Step B of Scheme 1)

The synthesis is based on Boyd, E.A.; Regan, A.C.; *Tetrahedron Lett* 24, 4223 (1994) as described in the previously filed patent 30012/PCT.

0.3 g (1.7 mmol) (4,4,4-trifluoro-butyl)-phosphinic acid 3b (0.3 g, 1.7 mmol) are dissolved in HMDS (1.4 g, 8.5 mmol) at room temperature and heated at 130°C for 4 h. At 80°C acrylate 1 (0.7g, 1.7 mmol) is added and the reaction mixture heated at 130°C for 16 h. Ethanol is added at 60°C and the mixture refluxed for 30 min. The solvents are removed under reduced pressure and the residue is dried at 50°C under high vacuum for 8 h to yield 0.9 g (89%) of 4b.

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Yield: 89 %.

Purity: ~80 % ($^1\text{H-NMR}$)

$^{31}\text{P-NMR}$ (CDCl_3 , 400MHz): 45.3 ppm (s).

MS (ESI neg.): 670 (8% [$\text{M} + \text{NaOAc} - \text{H}$], 588 (100% [$\text{M} - \text{H}$]).

$^1\text{H-NMR}$ (CDCl_3 , 400MHz): 1.2 (t, 3H), 1.55 (m, 2H), 1.7 (m, 1H), 1.8 (3H), 1.95 (m, 1H), 2.15 (3H), 2.2 (m, 1H), 2.4 (m, 1H), 2.75 (m, 1H), 4.1 (q, 2H), 6.8 (s, 1H, NH), 7.2 (Trityl-H).

Whereas this synthesis is described with reference to the "R" residue relating to compound 5b (above), this synthesis is carried out for the preparation of other alkyl or aralkyl phosphinic acids whose "R" residues correspond to the compounds 5a, 5c, 5f 5i, 5n, 5t, 5u, 5v, 5w, 5x, 5y and 5z (all described above).

Example 3:

Preparation of 2-[Hydroxy-(1,1,3,3-tetramethyl-indan-5-ylmethyl)-phosphinoylmethyl]-4-(trityl-carbamoyl)-butyric acid ethyl ester (4l) (Step C of Scheme 1)

This synthesis is based on a similar BSA-mediated alkylation of an alkylphosphinic acid described by L.A.Reiter, B.P.Jones, *J.Org.Chem.* 62, 2808 (1997).

In a 100mL flask equipped with a septum and a condenser, monoalkylphosphinic acid 2 (3g, 6.4 mmol) is dissolved in dry CH_2Cl_2 (20 ml). 5-Bromomethyl-1,1,3,3-tetramethyl-indan 6l (1.9g, 7 mmol) and BSA (3.9g, 19 mmol) are added and the mixture is stirred 72 h at 25°C. Work-up: The mixture is poured on 1N HCl. The organic phase is washed with 1N HCl, the combined acidic phases are re-extracted with 1N HCl. The combined organic phases are dried over MgSO_4 , evaporated under reduced pressure and dried at 50°C under high vacuum to give 4.77 g (100%) of the bisalkylated phosphinic acid 4l.

Yield: 100%

Purity: 82 % ($^{31}\text{P-NMR}$)

$^{31}\text{P-NMR}$ (CDCl_3 , 400MHz): 53.8 ppm (s).

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MS (ESI neg.): 1329 (10% [2M - H]), 664 (100% [M - H]), 494 (30%).

¹H-NMR (CDCl₃, 400MHz): 1.2 (t, 3H), 1.3 (14H), 1.7 (m, 1H), 1.9 (d, 2H, P-CH₂), 2.1 (m, 1H), 2.25 (2H), 2.7 (m, 1H), 3.0 (d, 2H, P-CH₂), 4.1 (q, 2H, OCH₂), 6.85 (s, 1H, NH), 7.2 (15H, trityl-H), 8.4 (s, 1H, P-OH).

Whereas this synthesis is described with reference to the "R" residue relating to compound 5l (above), this synthesis is carried out for the preparation of other benzylic or allylic phosphinic acids whose "R" residues correspond to the compounds 5d, 5e, 5g, 5h, 5j, 5k, 5m, 5o, 5p, 5q, 5r and 5s (all described above).

Example 4

Hydrolysis / detritylation of bisalkyl-phosphinoyl compounds 4 to the P-alkylated 2-(Alkyl-hydroxy-phosphinoylmethyl)-4-carbamoyl-butyric acids 5: (Steps D and E in Scheme 1)

A compound 4 (1g, 1.9 mmol) is solubilized in 9mL ethanol. 9mL 1N LiOH (5eq) are added. The reaction mixture is stirred 3h at room temperature. 1N HCl is added until pH=1 and EtOH is removed under reduced pressure. The aqueous residue is extracted with CH₂Cl₂. The organic layers are dried over MgSO₄. Evaporation of the combined organic layers gives 0.75 g of hydrolyzed intermediate. Complete Hydrolysis is checked by ¹H-NMR, the structure can be further confirmed by ³¹P-NMR and MS (ESI neg.). The material is subjected to detritylation without further purification:

The above acid (0.5g, 1mmol) is solubilized in 10mL TFA. 0.35 g (2.2mmol) iPr₃SiH are added via syringe. The reaction mixture is stirred for 2 h at room temperature. TFA is removed under reduced pressure and the reaction mixture co-evaporated with toluene. The crude product is dissolved in 7 ml water at 50°C and filtered over a RPC-18 syringe. The filtrate is co-evaporated with Toluene giving 0.1 g of 5 (42%).

All of the compounds 5 described above are obtained with purities: 85-90% (³¹P-NMR).

Example 5

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Preparation of 7-Bromomethyl-1,1,2,4,4-pentamethyl-1,2,3,4-tetrahydro-naphthalene
6j: (Step F of Scheme 2)

The solventless bromination of substituted toluenes at higher temperatures is based on well known literature methods, e.g. I.B.Shoesmith, A.Mackie, *J.Chem.Soc.*, 300 (1936) or J.B.Baker, *J.Chem.Soc.*, 1448 (1936).

In a 100mL flask equipped with thermometer, septum and a condenser 21.6 g (0.1 mol) 1,1,2,4,4,7-hexamethyl-1,2,3,4-tetrahydro-naphthalene (prepared as described by Wood, T. F.; Easter, W. M., Jr.; Carpenter, M. S.; Angiolini, *J. Org. Chem.* 28, 2248 (1963)) are heated to 170°C. 16 g (0.1 mol) Bromine are added and the reaction mixture is stirred for 5 h at 170°C. The content of the flask is fractionated over a Vigreux column (110°C, 0.04 Torr) giving 17 g (58%) 6j as a colorless liquid.

Yield: 58%.

GC-purity: 71%

Impurities:

7% 1,1,2,4,4,7-hexamethyl-1,2,3,4-tetrahydro-naphthalene

14% 7-Dibromomethyl-1,1,2,4,4-pentamethyl-1,2,3,4-tetrahydro-naphthalene

GC/MS: 294 / 296 (5%, $[M]^+$), 279 / 281 (10%, $[M - CH_3]^+$), 215 (100%, $[M - Br]^+$), 201 (65%, $[M - CH_2Br]^+$), 157 (55%).

1H -NMR ($CDCl_3$, 400MHz): 0.95 (d, 3H), 1.05 (s, 3H), 1.25 (s, 3H), 1.3 (s, 3H), 1.35 (s, 3H), 1.4 (dd, 1H, A), 1.65 (dd, 1H, B), 1.85 (m, 1H, CH), 4.5 (s, 2H, CH_2Br), 7.15 (d, 1H, Ar-H), 7.25 (d, 1H, Ar-H), 7.35 (s, 1H, Ar-H).

^{13}C -NMR ($CDCl_3$, 400MHz): 16.8 (CH_3), 25.0 (CH_3), 28.5 (CH_3), 31.9 (CH_3), 32.3 (CH_3), 34.3 (CH_2), 34.4 (C), 34.5 (CH), 37.8 (C), 43.5 (CH_2Br), 126.2, 127.0, 127.7 (Ar-CH), 134.7, 145.2, 146.5 (Ar-C).

Example 6

Preparation of (5-Iodo-3-methyl-pentyl)-benzene 7c: (Step G of Scheme 2)

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The synthesis proceeded according to the well known literature method, see for example M.Ishizaki, O.Hoshino et al., *Tetrahedron* 57, 2729 (2001).

5 g (28 mmol) Phenoxanol (3-Methyl-5-phenyl-pentan-1-ol) are dissolved in 200 ml dichloromethane under nitrogen and stirring. Triphenylphosphine (8.8 g, 34 mmol) and 4.2 g (53 mmol) pyridine are added at 25°C. At 0°C iodine (8.5 g, 34 mmol) are added. After 2 h stirring at 0°C the reaction mixture is poured on ice-cooled 1 N HCl and extracted with dichloromethane. The combined organic phases are washed with 10% Na₂S₂O₃, sat. NaHCO₃ and sat. NaCl. Drying over MgSO₄ and evaporation gives 17g of a residue which is triturated with hexane and filtered over a 5 cm Silicagel pad. The filtrate is evaporated under reduced pressure and dried under high vacuum giving 7.1 g (88%) of 7c as an colorless oil.

Yield: 88%.

Purity: > 95% (GC, NMR)

GC/MS: 288 (5%, [M]⁺), 161 (10%, [M - I]⁺),

119 (5%), 105 (20%, [PhCH₂CH₂]⁺), 91 (100%, [[PhCH₂]⁺).

¹H-NMR (CDCl₃, 400MHz): 0.95 (d, 3H, CH₃), 1.45 (m, 1H), 1.6 (3H), 1.9 (m, 1H), 2.6 (2H, PhCH₂), 3.2 (2H, CH₂I), 7.2 (5H, ArH).

¹³C-NMR (CDCl₃, 400MHz): 4.9 (CH₂), 18.7 (CH₃), 33.3 (CH₂), 33.7 (CH₃), 38.2 (CH₂), 40.9 (CH₂), 125.8, 128.3, 128.4 (ArCH), 142.5 (ArC).

Example 7

Preparation of E-1-(3-Bromo-2-methyl-propenyl)-4-tert-butyl-benzene 8o: (Steps H and I of Scheme 2)

Both steps are well known literature methods, e.g. R.M.Coates, D.A.Ley, P.L.Cavender, *J.Org.Chem.* 43, 4918 (1978).

20 g (0.1 mol) E-3-(4-tert-Butyl-phenyl)-2-methyl-propenal (prepared as described at Y.Cramer, P.A.Ochsner, P. Schudel, US 4435585, Givaudan (1982)) are added to a

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stirred solution of 1.2 g (32 mmol) of sodium borohydride in 20 ml of methanol at 0°C. After 2 h at room temperature quantitative conversion is checked by TLC. The reaction mixture is poured onto 40 ml saturated sodium chloride and extracted with tert-butyl methyl ether. Drying over magnesium sulfate and evaporation of the solvent gives the crude allylic alcohol (19.2 g, 94%), which is transferred to the following bromination without further purification.

5 g (24 mmol) of the crude allylic alcohol are dissolved in 35 ml of dry diethyl ether under nitrogen. At 0°C phosphorus tribromide (0.95 ml, 10 mmol) is added via syringe. The reaction is stirred at 0°C for 4 h, poured onto ice and extracted three times with diethyl ether. The organic layer is washed with saturated NaHCO₃ and dried over MgSO₄. The solvent is removed under reduced pressure giving the crude allylic bromide 5.7 g (87%) of 8o.

Yield: 5.7 g (82% from the aldehyde).

Purity: > 95% (GC, NMR)

GC/MS: 266 / 268 (3%, [M]⁺), 251 (1%, [M - CH₃]⁺), 188 (25%, [M - Br]⁺), 173 (55%, [M - Br - CH₃]⁺), 157 (10%), 131 (55%), 115 (22%), 91 (16%), 57 (100%).

¹H-NMR (CDCl₃, 400MHz): 1.3 (s, 9H, tBu-CH₃), 2.0 (s, 3H, CH₃), 4.15 (s, 2H, CH₂Br), 6.6 (s, 1H, =CH), 7.22 (d, 2H, Ar-H), 7.35 (s, 2H, Ar-H).

¹³C-NMR (CDCl₃, 400MHz): 16.6 (CH₃), 31.3 (3C, tBu-CH₃), 34.6 (tBu-C), 42.6 (CH₂), 125.2, 128.7 (ArCH), 130.0 (=CH), 133.7, 134.0 (Ar-C), 150.2 (=C)

Example 8

Preparation of (3,7-Dimethyl-octa-2,6-dienyl)-phosphinic acid 3n: (Step K of Scheme 2)

Synthesis is based on the publication of E.A.Boyd, A.C.Regan, *Tetrahedron Letters*, 24, 4223 (1994). Recently it has been found that a 3-5 eq excess of the reagents HMDS and ammonium phosphinate improves the yield of alkyl phosphinic acid 3 formation when alkyl iodides 7 are employed (H.An et al., *J.Org.Chem.* 66, 2789 (2001), S.Chern, J.K.Coward, *J.Org.Chem.* 63, 502 (1998)) and that an excess of HMDS

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and $\text{NH}_4^+\text{PO}_2\text{H}_2^-$ prevents also bis-alkylation using benzylic- or allylic bromides 6 or 8 (S.Depréle, J.-L.Montchamp, *J.Org.Chem.* 66, 6745 (2001)).

In a 750mL flask equipped with septum, thermometer and condenser, ammonium phosphinate (25 g, 0.3 mol) and HMDS (51 g, 0.32 mmol) are heated under N_2 at 110°C for 3 h. The reaction mixture is cooled to 0°C . 300 mL dried CH_2Cl_2 are added followed by the addition of geranyl bromide (13.1 g, 60 mmol). The mixture is stirred for 16 h at room temperature. 12 g methanol are added and the fine suspension is filtered over a double filter layer. The filtrate is concentrated under reduced pressure. 10% Na_2CO_3 and *tert*-butyl methyl ether are added, the phases are separated and the alkaline layer purified with *tert*-butyl methyl ether. The alkaline layer is treated with conc. HCl until $\text{pH} = 1$ and is 3 times extracted with dichloromethane. Drying of the dichloromethane layer over MgSO_4 and evaporation give 13.7 g (81%) of **3n** as an orange oil.

Yield: 13.7 g (81%).

Purity: 77% (^{31}P -NMR)

^{31}P -NMR (CDCl_3 , 400MHz): 34.9 ppm (s).

MS (ESI neg.): 403 (10% $[\text{2M} - \text{H}]^+$), 201 (100%, $[\text{M} - \text{H}]^+$).

^1H -NMR (CDCl_3 , 400MHz): 1.2 (d, 1H), 1.6 (s, 3H, CH_3), 1.6 (6H, 2 CH_3), 2.1 (4H, CH_2CH_2), 2.6 (dd, 2H, P- CH_2), 5.1 (1H, =CH), 5.15 (1H, =CH), 6.22 and 7.6 (d, 1H, $J = 548 \text{ Hz}$, P-H), 11.8 (s, 1H, POH).

^{13}C -NMR (CDCl_3 , 400MHz): 16.5 (CH_3), 17.6 (CH_3), 25.6 (CH_3), 26.4 (CH_2), 30.4 and 29.5 (d, P- CH_2), 39.7 (CH_2), 110.5 (=CH), 123.7 (=CH), 131.7 (=C), 141.9 (=C).

Example 9

Preparation of (3-phenyl-propyl)-phosphinic acid **3t**: (Step L of Scheme 2)

The method has been described by S. S.Depréle, J.-L.Montchamp, *J.Org.Chem.* 66, 6745 (2001).

To a solution of $\text{NaH}_2\text{PO}_2(\text{H}_2\text{O})$ (13.2 g, 0.125 mol) and allylbenzene (6.6 g, 56 mmol) in methanol (250 ml) is added triethylborane (1M in THF, 50 ml, 50 mmol) at room

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temperature in an open 500 ml flask. The solution is stirred for 2 h at room temperature. The reaction mixture is concentrated under reduced pressure. 100 ml saturated KHSO_4 are added to the residue followed by extraction (200, 100 and 70 ml) with ethyl acetate. To the combined ethyl acetate phases are added 40 ml 10% Na_2CO_3 . Under vigorous stirring and dropwise addition of conc. NaOH the biphasic mixture is adjusted to $\text{pH} = 10$. The organic phase is separated and the alkaline phase adjusted to $\text{pH} = 2$ by addition of conc. HCl . Extraction with chloroform (3 x 100 ml), drying of the combined organic layer over MgSO_4 and evaporation gives 5.4 g of crude **3t** (61%).

Yield: 61%

Purity: 84% (^{31}P -NMR)

^{31}P -NMR (CDCl_3 , 400MHz): 38.2 ppm (s).

MS (ESI neg.): 265 (6% $[\text{M} - \text{H} - \text{NaOAc}]^+$), 183 (100%, $[\text{M} - \text{H}]^+$).

^1H -NMR (CDCl_3 , 400MHz): 1.75 (m, 2H, CH_2), 1.9 (m, 2H, CH_2), 2.76 (t, 2H, PhCH_2), 6.4 and 7.7 (d, 1H, $J = 548 \text{ Hz}$, P-H), 11.4 (s, 1H, POH).

Application Examples

Example 1,

Isolation of new malodour acid and precursors thereof from human sweat:

Fresh axilla secretions are sampled from human panellists by washing the axilla with 10% ethanol. The samples are extracted with MTBE to remove interfering lipids. The hydrophilic phases obtained from the washings from several individuals are then pooled. This material is practically odourless, but upon hydrolysis of sub-samples with 1 M NaOH , it produced typical axilla malodour. To identify the malodour volatiles, hydrolysed sub-samples are extracted and concentrated by solid phase extraction and then analysed by GC-sniff. Peaks that are rated as having a strong odour and closely related to axilla malodour are analysed by GC-MS. The samples contained one particular peak of an acid very typical of axilla malodour. Based on the MS data the most probable structure of this peak is 3-hydroxy-3-methyl-hexanoic acid. This assumption is verified by synthesising this latter compound and comparing its spectra

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and retention times to the GC-MS data of the major malodour peak in the GC-sniff analysis. This malodour compound is structurally related to the known sweat malodour acid 3-methyl-2-hexenoic acid, and it is transformed into this latter compound by dehydration upon prolonged incubation.

To identify the precursor for this acid, the pooled non-hydrolysed sample is separated on a Superdex gel filtration column (Pharmacia, Uppsala, Sweden) using $\text{NH}_4\text{CO}_3/\text{NaCl}$ as the elution buffer. Individual fractions of this separation step are tested for the content of a malodour precursor by hydrolysis with 1 M NaOH. One fraction developed strong malodour upon hydrolysis and this malodour could be attributed to the release of 3-hydroxy-3-methyl-hexanoic acid by GC-MS analysis. This fraction is subjected to LC-MS analysis. It contained one major mass peak of 274 Da and an additional peak at 256 Da. The mass spectrum of the former peak suggested a compound where the 3-hydroxy-3-methyl-hexanoic acid is linked to one molecule of L-glutamine (i.e. N_α -3-hydroxy-3-methyl-hexanoyl-L-glutamine), while the second peak could, based on its mass, correspond to the dehydrated analogue N_α -3-methyl-2-hexenoyl-L-glutamine. N_α -3-hydroxy-3-methyl-hexanoyl-L-glutamine is then synthesised and its MS spectrum and retention time in the LC-MS-analysis compared to and found identical with the compound isolated from natural sweat.

Example 2

Isolation of axilla bacteria having the ability to cleave the malodour precursor compound

The axillary flora of 8 panellists is isolated with the detergent-scrub method: A 6 cm² area of the axilla is scrubbed with a phosphate buffer at pH 7 containing 1% Tween 80. The samples are spread-plated on tryptic soy agar amended with 5g/L of Tween 80 and 1 g/L of lecithin. Single isolates obtained after 48 h incubation are subcultured and characterised. A total of 24 individual strains are identified based on colony and cell morphology, gram-reaction, lipophilic growth, lipase reaction and API identification kits (bioMerieux, France; coryneforms with the API coryne kit and cocci with the ID

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Staph 32 kit). The strains are grown overnight in a liquid medium (Mueller-Hinton amended with 0.01% Tween 80), harvested by centrifugation and resuspended to a final OD₆₀₀ of 1 in a semi-synthetic medium (Per litre: 3 g KH₂PO₄, 1.9 g K₂HPO₄, 0.2 g yeast extract, 0.2 g MgSO₄, 1.4 g NaCl, 1 g NH₄Cl, 10 mg MnCl₂, 1 mg Fe₃Cl₂, 1 mg CaCl₂). Aliquots of this stationary culture are then amended with a final concentration of 500ppm of N α -3-hydroxy-3-methyl-hexanoyl-L-glutamine (5% stock solution dissolved in methanol). After 24 h incubation (with shaking at 300rpm; 36°C) the samples are extracted and the amount of released 3-hydroxy-3-methyl-hexanoic acid is determined by capillary GC. Table 1 gives the results for a subset of the strains tested. From these results it appears that among the *Corynebacteria* isolated from the axilla some, but not all, are able to release 3-hydroxy-3-methyl-hexanoic acid from the synthetic precursor. The *Corynebacteria* which are able to conduct this biochemical reaction may be found in the group of the lipophilic and in the group of the non-lipophilic *Corynebacteria*. Therefore, a specific enzyme only present in some bacterial strains seems to be responsible for this cleavage. Since it releases axilla malodour the putative enzyme is named AMRE, which stands for 'axillary malodour releasing enzyme'. Apparently the tested *Staphylococci* are not able to catalyse this reaction, which is in agreement with the observation, that only subjects with an axilla flora dominated by *Corynebacteria* produce the most typical axilla malodour (Labows *et. al.*; Cosmet. Sci Technol. Ser. 1999, 20:59-82). However, when N α -lauroyl-L-glutamine is used as substrate in the same experiment, it is found that also other *Corynebacteria* and some *Staphylococci* can release lauric acid from this substrate. It therefore appears, that most axilla bacteria have a related enzyme, but that many can only release straight fatty acids which make a minor contribution to typical axilla malodour.

Table 1. Cleavage of the natural malodour precursor by axilla bacteria.

| Isolate | Species assignment | Lipophilic (*) | 3-hydroxy-3-methyl-hexanoic acid released (ppm) |
|---------|-----------------------------------|-------------------|----------------------------------------------------|
| Ax1 | <i>Staphylococcus capitis</i> | - | 0 |
| Ax6 | <i>Staphylococcus epidermidis</i> | - | 0 |
| Ax9 | <i>Micrococcus luteus</i> | - | 0 |
| Ax3 | <i>Corynebacterium bovis</i> | + | 0 |

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| | | | |
|------|---------------------------------|---|-------|
| Ax7 | <i>Corynebacterium group G</i> | + | 0 |
| Ax15 | <i>Corynebacterium jeikeium</i> | + | 37.4 |
| Ax19 | <i>Corynebacterium jeikeium</i> | + | 105.1 |
| Ax20 | <i>Corynebacterium striatum</i> | - | 262.7 |

(*) *Corynebacteria* isolated from the human axilla may be separated into two classes based on their requirement for a source of fatty acids in the growth medium.

Example 3

Purification and analysis of the enzyme from strains that cleave malodour precursor compounds:

Corynebacterium striatum Ax20 is selected to isolate and purify the enzyme responsible for the cleavage of the precursor α -3-hydroxy-3-methyl-hexanoyl-L-glutamine. The strain is grown during 48 h in Mueller-Hinton broth amended with 0.01% Tween 80. A total volume of 2 L of culture is harvested by centrifugation. The pellet is washed in Buffer A (50mM NaCl; 50 mM $\text{NaH}_2\text{PO}_4/\text{K}_2\text{HPO}_4$ buffer at pH 7) and this buffer is used throughout the whole purification procedure. The cells are disrupted mechanically by vortexing them with glass beads (425-600 μm , Sigma, St-Louis, USA) during 30 min at maximal speed. The crude cell lysate is then fractionated by precipitation with an increasing concentration of $(\text{NH}_4)_2\text{SO}_4$. The precipitate obtained between 50% and 80% saturation of $(\text{NH}_4)_2\text{SO}_4$ contained the active enzyme. This enriched sample is dissolved in Buffer A and then sequentially passed over four chromatography columns: DEAE Sepharose CL-6B anion exchange resin (Pharmacia, Uppsala, Sweden; elution with a linear gradient from 0 to 800 mM KCl); Phenyl-Sepharose hydrophobic interaction resin (Pharmacia; elution with a linear gradient from 1000 mM to 0 mM of $(\text{NH}_4)_2\text{SO}_4$; Mono Q strong anion exchange column on the FPLC system (Pharmacia; elution with a gradient from 0 to 800 mM KCl) and finally Mono P weak anion exchange column on the FPLC (elution with a gradient from 0- 800mM KCl in a 50 mM Bis-Tris buffer instead of Buffer A). After each column separation the active fractions (determined by fluorescent activity assay with α -lauroyl-L-glutamine as substrate) are pooled and then desalted and concentrated by ultrafiltration (Amicon membrane YM10, Millipore, Bedford, US). The resulting active fractions after the last column separation contained

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one major protein band with an apparent molecular weight of about 48kDa as determined by SDS-PAGE. Its effective molecular mass is determined by nano-ESI MS analysis and found to be 43365 ± 5 Da. This enzyme retains all its activity if incubated with PMSF (Phenylmethylsulfonylfluoride, Roche Biochemicals, Mannheim, Germany) and Pefabloc SC (4-(2-aminoethyl)-benzenesulfonylfluoride, Roche Biochemicals), which are typical inhibitors for serin- and cystein proteases. On the other hand it is completely inhibited by 1 mM of EDTA and o-phenantrolin. This inhibition can be reversed by the addition of 1mM $ZnCl_2$.

Example 4

Measuring inhibitory activity

Extracts of Ax 20 are prepared by mechanical disruption as described in Application Example 3.

The extract (50 μ l ml corresponding to 0.2 ml initial cell culture) is added to 50 μ l of Buffer A. Various concentrations of the compounds of the present invention are added in a volume of 40 μ l, and after 10 min preincubation at 37°C, the reaction is amended with 10 μ l of substrate (N α -lauroyl-L-glutamine, final concentration 50 μ M). The samples are incubated for 15 min and then the reaction is stopped by adding 75 μ l of Fluorescamine (2.5 mM dissolved in Acetonitrile). The resulting fluorescence resulting from derivatization of the released glutamine with fluorescamine is determined at an excitation wavelength of 381 nm and an emission wavelength of 470 nm. By comparing the samples containing compounds of the present invention with control samples with enzyme and substrate only, the inhibition (%) is calculated. Alternatively, the same assay is made either with purified enzyme from the wild-type strain (see example 3) or with a recombinantly formed enzyme produced with a strain containing an expression vector comprising a nucleic acid sequence encoding for the enzyme. Compounds of the present invention tested with this method show inhibitor activity in the nano-molar to tens of nano-molar range.

In order to evaluate enzyme activity in intact cells, stationary phase living cells of Ax20 are harvested and resuspended in Buffer A to an optical density at 600 nm of 0.25.

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Inhibitory compounds are added at various concentrations, and after a preincubation of 15 min, the substrate (N α -lauroyl-L-glutamine, 1 mM final concentration) is added. The samples are incubated for 1 h and then extracted with MTBE and HCl and analysed for released lauric acid using capillary GC. By comparing the samples containing compounds of the present invention with control samples with bacteria and substrate only, the inhibition (%) is calculated. By comparing the inhibitory capacity of the compounds on the isolated enzyme with the values obtained using intact cells, the relative uptake of the compounds by the cells can be assessed. The compounds of the present invention can cross the bacterial cell wall and cytoplasmatic membrane, and thus can have inhibitory activity in living cells at a concentration below 1 μ M.

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Sequence listing part of description

SEQUENCE LISTING

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<212> PRT

<213> Corynebacterium striatum

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20 25 30

Ser Met Gln Glu His Glu Thr Ser Lys Arg Ile Ala Glu Glu Leu Glu
35 40 45

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Val Ile Lys Asn Gly Glu Gly Pro Ser Val Ala Phe Arg Ala Asp Phe
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Asp Ala Leu Pro Ile Thr Glu Asn Thr Gly Leu Asp Tyr Ser Ala Asp
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Pro Glu Leu Gly Met Met His Ala Cys Gly His Asp Leu His Thr Thr
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Ala Leu Leu Gly Ala Val Arg Ala Leu Val Glu Asn Lys Asp Leu Trp
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Ser Gly Thr Phe Ile Ala Val His Gln Pro Gly Glu Glu Gly Gly Gly
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Gly Ala Arg His Met Val Asp Asp Gly Leu Ala Glu Lys Ile Ala Ala
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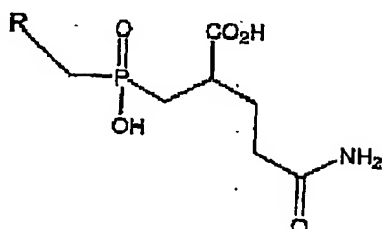
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Claims

1. A compound of formula (I)



wherein

R is a substituted alkyl, benzyl or allyl residue selected from the group consisting of
nonyl;

4,4,4-trifluoro-propyl;

2-methyl-4-phenyl-butyl;

4-trifluoromethyl-phenyl;

pentafluorophenyl;

4-fluoro-phenyl;

naphthalene-2-yl;

biphenyl-2-yl;

4-tert-butyl-phenyl;

5,5,7,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalene-2-yl;

5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl;

1,1,3,3-tetramethyl-indan-5-yl;

styryl;

2,6-dimethyl-hept-1,5-dienyl;

2-(4-tert-Butyl-phenyl)-1-methyl-vinyl;

2-(4-Isopropyl-phenyl)-1-methyl-vinyl;

1-Methyl-3-(2,2,3-trimethyl-cyclopent-3-enyl)-propenyl;

2-(4-Isobutyl-phenyl)-1-methyl-vinyl;

2-(2-isopropyl-phenyl)-1-methyl-ethenyl;

2-phenyl-ethyl;

cyclohexyl-methyl;

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2,2-dimethyl-propyl;

2-pentafluorophenyl-ethyl;

3-phenyl-propyl; heptyl; and

4-isopropyl-cyclohex-1-enyl.

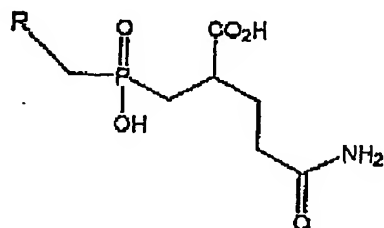
2. A composition comprising a body odour-suppressing quantity of a compound claimed in claim 1.
3. Composition according to claim 2 wherein the compound is present in amounts of about 0.01 to 0.5 % by weight.
4. Composition according to claim 2 or claim 3 selected from cosmetic and personal care products, in particular deo-sticks, roll-ons, pump-sprays, aerosols, deodorant soaps, powders, solutions, gels, creams, sticks, balms and lotions.
5. Use of a compound or composition to inhibit an enzyme in its ability to cleave compounds contained in sweat into short-chained, branched fatty acids, which enzyme is produced in bacteria of the genus *Corynebacteria*, which bacteria has been deposited at the International Depository Authority DSMZ- Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH, D-38124 Braunschweig under the Accession Number DSM 14267.
6. Use of a compound or composition to inhibit an enzyme in its ability to cleave compounds contained in sweat into short-chained, branched fatty acids, which enzyme is defined by an amino acid sequence set forth as SEQ ID No. 1.
7. A method of suppressing axillary malodour comprising the step of providing a composition for application to a person in need of treatment, said composition containing an inhibitor compound and a dermatologically acceptable vehicle therefor, said compound being selected from a screening of compounds for activity in the inhibition of the enzyme.

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Abstract

Inhibitors of axillary malodour having the formula



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